Remarks

Claims 22-25, 27-31, 33-34, and 36-38 are pending in the application. Claim 1-21, 26, 32, 35 and 39-47 have been cancelled without prejudice or disclaimer. Claim 22 has been amended as recommended by the Examiner to recite "hemoglobin" before "Hb".

Rejections under 35 U.S.C. § 103

Claims 22-25, 27-31, 33, 34, and 36-38 stand rejected under 35 U.S.C. § 103 as obvious over Gould, *et al.*, J. Trauma: Injury, Infection and Critical Care 43(2):325-332 (1997) taken with DeWoskin *et al.* (U.S. Patent No. 6,498,141) and Seghal, *et al.,* Surgery 95(4):433-438 (1984).

In the Office Action, the Examiner relies upon DeWoskin *et al.,* which teaches the administration of "up to at least about 5 L" of a polymerized hemoglobin solution. According to the Examiner, one of ordinary skill in the art would have been motivated to incorporate the administration of a large volume of hemoglobin solution as taught by DeWoskin *et al.* to patients who are suffering from hemorrhage as taught by Gould, *et al.*. The Examiner finds that one of skill in the art would have been motivated to employ large volumes of hemoglobin solutions because of DeWoskin *et al.*'s teaching that the solution does not cause vasoconstriction, renal toxicity, hemoglobinura and other problems implicated with intravenous administration of known hemoglobin solutions containing undesirable amounts of tetrameric hemoglobin.

Applicants respectfully disagree with the Examiner's conclusion. Attached hereto as Exhibit A is *Gould, et al., The Life-Sustaining Capacity of Human Polymerized Hemoglobin when Red Cells Might Be Unavailable,* J. Amer. Coll. Surg. (2002) 195(4):445-455 (hereinafter "Gould 2002"). This article reports the experimental data that is found in the specification

regarding the life sustaining properties of high volume administration of hemoglobin solutions. Following the article is a comment of Dr. Ronald Maier, Professor of Trauma Surgery and Vice Chairman, Surgeon-in-Chief, Harborview Medical Center, University of Washington. A copy of Dr. Maier's CV is attached as Exhibit B. In his comment, Dr. Maier confirms that at the time of the invention one of skill in the art would not have been motivated to use high volumes of hemoglobin solutions:

> [t]he authors collected extensive posttransfusion data to confirm absence of toxicity, particularly for the well-recognized problems caused by other hemoglobin solutions in renal, hepatic, and cardiac function. ... **[B]ased upon severity of injury, blood loss, transfusion volume and other factors, one would predict that the multiple organ failure rates would have been significant in this patient population.** Yet in the current study there is *no* organ dysfunction.

Id., p. 453, right column (bold emphasis added, italics in original).

Given this teaching, its clear that one of skill in the art at the time of the invention would have not have concluded as the Examiner now does through hindsight that the use of polymerized hemoglobin solutions could be used to treat massive blood loss. The Examiner cites to a number of cases that suggest that the references must be considered in their entirety, and not individually. Indeed, the totality of the prior art must be considered. See MPEP § 2145 X. D. 3. Proceeding contrary to the accepted wisdom in the art is evidence of non-obviousness. *Id.* The comment of Dr. Maier in *Gould, et al.*, 2002 shows that that one of skill in the art would have expected multiple organ failure as a result of the use of the present invention. The applicants proceeded against the conventional wisdom in the art and their success was not expected.

Dr. Maier's comments show that what is missing from the Examiner's analysis is a showing that a skilled artisan, reading the cited references, would have a reasonable expectation

of success in using a hemoglobin solution for treating patients with massive blood loss. The Examiner points the teaching in Seghal, *et al.* regarding the delivery of less than one liter of solution to baboons. This teaching, however, does not suggest the invention when considering the totality of the prior art. As applicants pointed out previously, Sehgal, *et al.* teaches that the "clinically appropriate intravascular persistence for a red blood cell substitute is unclear" and "these data cannot be extended to the clinical setting." (p. 437, first column, second paragraph). This section of Seghal, *et al.* "suggest that poly SFH-P will be effective as an acelluar O_2 carrier, its efficacy will have to be confirmed ... ." (*Id.*) Indeed, Seghal, *et al.* identifies a number of issues that remain to be addressed including "nephrotoxicity, immunogenicity and the effect on the reticuloendothelial system." (*Id.*, top of second column). Seghal, *et al.* is consistent with Dr. Maier's comment that one of skill in the art would have expected significant organ failure when dosed with volumes of hemoglobin solution greater than 5 L. Therefore, the totality of the prior art fails provide the skilled artisan with a reasonable expectation of success with the method of the claimed invention. Accordingly, the invention is not obvious. Therefore, Applicants request that the rejection to these claims under 35 U.S.C. § 103 be withdrawn.

CONCLUSION

There may be other reasons for patentability for independent claims 22 and 30 and the dependent claims, and Applicants do not waive those arguments by failing to assert those arguments here. Applicants view the foregoing reasons as sufficient to establish that the claims are novel and nonobvious, but expressly reserve the right to make further argument regarding patentability of the claims.

With the above Amendments and Remarks, the Applicants respectfully submit that the application is now in a condition for allowance. If the Examiner is of the opinion that a telephone conference would expedite prosecution of the application, the Examiner is encouraged to contact Applicants' undersigned representative.

Respectfully submitted,

McDONNELL BOEHNEN HULBERT & BERGHOFF LLP

By: _____

Patrick G. Gattari
Reg. No. 39,682

300 South Wacker Drive
32nd Floor
Chicago, Illinois 60606
312-913-0001 (telephone)
312-913-0002 (facsimile)